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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/448,378	11/23/1999	KENNETH BRASEL	2836-D	4973
22932	7590	11/05/2003	EXAMINER	
IMMUNEX CORPORATION LAW DEPARTMENT 51 UNIVERSITY STREET SEATTLE, WA 98101			GAMBEL, PHILLIP	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/448,378	Applicant(s) BRASEL ET AL.	
	Examiner Phillip Gambel	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6, 7, 20 and 23-56 is/are pending in the application.
- 4a) Of the above claim(s) 54-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6, 7, 20, 23-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☒ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment, filed 7/28/03, has been entered.
Claims 1-5, 8-19, 21, have been canceled previously.
Claims 25 and 34 have been amended.

Claims 6-7, 20 and 22-56 are pending.

Applicant's remarks that claim 7 has been withdrawn to facilitate prosecution is not understood.

Applicant's election without traverse of Group I and the species GM-CSF in Paper No. 21, filed 1/4/02, and Paper No. 23, filed 11/13/02, has been acknowledged.

As indicated previously, claims 6, 7, 20 and 22-53 read on the elected invention and have been acted upon.

Claim 7 remains under consideration in the instant application.

Claims 54-56 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendment, filed 7/28/03.
The rejections of record can be found in previous Office Action, mailed 1/24/03.

Given the absence of additional rebuttal to the outstanding rejections of record in applicant's amendment, filed 7/28/03; the rejections are maintained for the reasons of record

3. As pointed out previously, it appears that the filing date of the instant claims is deemed to be the filing date of the priority application USSN 08/539,142, i.e. 10/4/95.

4. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 25 and 34 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed for the reasons set forth in the previous Office Action, mailed 1/24/03.

There is insufficient written description encompassing "a soluble human flt3-ligand ... is at least 90% identical ... " because there is insufficient written description as to the identity of a flt3-ligand that "at least 90% identical" as set forth in claims 25 and 34 and that would still maintain the function of the polypeptide. Polypeptides having diverse functions are encompassed by the phrase "at least 90% sequence identity" as set forth in claims 25 and 34. Further, there is no requirement that the identity extend over the full length of the polypeptide. Thus a broad genus having potentially highly diverse functions is encompassed by the phrase "at least 90% sequence identity" and conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses employing any "flt3-ligand that is at least 90% identical" set forth in claim 25, yet the instant specification and the priority applications do not provide sufficient written description as to the structural features of any "at least 90% identical flt3-ligand" and the correlation between the chemical structure and the function of the genus of "at least 90% flt3-ligands". The reliance on the disclosed limited examples of the "at least 90% flt3-ligands" in the specification as-filed and the priority applications does not support the written description of any "at least 90% identical flt3-ligand".

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying a "flt3-ligand", encompassed by the claimed specificity and, in turn, would be sufficient to generate an increase in the number of dendritic cells in order to augment an immune response or treat cancer.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the certain "flt3-ligands" disclosed in the specification as-filed and the priority applications does not appear to provide sufficient written description for "at least 80% identical flt3-ligands" encompassed by the claimed methods.

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "at least 90% identical flt3-ligands" set forth in claims 25 and 34. The specification nor the priority applications do not disclose nor identify "flt3-ligands" other than those disclosed in this application and priority applications.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "at least 80% identical flt3-ligands" as set forth in claims 25 and 34; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

5. Claims 6, 7, 20 and 22-53 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lyman et al. (U.S. patent No. 5,843,423; 1449) in view of Elliott et al. (U.S. Patent No. 5,478,556), Srivastava et al. (U.S. Patent No. 6,017,544) and Brem et al. (U.S. Patent No. 5,626,862) for the reasons set forth in the previous Office Action, mailed 1/24/03.

As pointed out above, applicant's remarks, filed 7/28/03, that claim 7 has been withdrawn to facilitate prosecution is not understood.

Applicant's election without traverse of Group I and the species GM-CSF in Paper No. 21, filed 1/4/02, and Paper No. 23, filed 11/13/02, has been acknowledged.

As indicated previously, claims 6, 7, 20 and 22-53 read on the elected invention and have been acted upon.

Claim 7 remains under consideration in the instant application.

The instant claims are drawn to methods of augmenting immune responses in cancer patients with FLT3-ligand and GM-CSF.

Lyman et al. teach methods of treating cancer patients by administering FLT3-L in combination with other cytokines, including GM-CSF including treating intestinal damage resulting from irradiation and chemotherapy and stimulating immune responses as well as hemopoietic cells to improve the quality of life of a patient (see entire document; Background of the Invention; Summary of the Invention, including column 3, paragraph 4; column 7; and Claims). Lyman et al. teach the FLT3-L and its recombinant forms and sequences encompassed by the claimed invention (See Detailed Description of the Invention, particularly columns 8-11 and Examples).

Lyman et al. differs from the claimed methods by not disclosing the known administration of a tumor antigen to a cancer patient to induce an immune response to the desired tumor antigen and that the administration of FLT3-L and/or GM-CSF would lead to an increase in the number of dendritic cells per se.

Both Elliott et al. and Srivastava teach that GM-CSF teach the known administration of GM-CSF with tumor antigens to simulate the immune system.

Elliott et al. teach the vaccination of cancer patients with tumor associated antigens mixed with cytokines, including GM-CSF, including the stimulation of antigen-processing (see entire document, Background of the Invention, Summary of the Invention, Detailed Description of the Invention). Both the tumor associated antigens and the GM-CSF can be administered at various times (see Summary of the Invention).

Srivastava teach methods of augmenting cancer vaccines with cytokines including GM-CSF (see entire document; including Summary of the Invention, including column 4, paragraph 6; Detailed Description, including column 12, paragraph 3; Claims.). Srivastava teach compositions comprising cancer cells as well as cancer antigens serve as sources for immunization against tumor antigens of interest (See entire document, including Background of the Invention, Summary of the Invention and Detailed Description of the Invention). In addition to combining cancer therapies, including surgery, radiation therapy and chemotherapy (columns 5-6, overlapping paragraph), dosages and modes of administration depend on variables known and practiced in the art at the time the invention was made (e.g. see columns 11-12, Formulation and Administration of the Complexes). Srivastava teach that a number of tumor types, including fibrosarcoma, can treated (see column 6, paragraphs 4-5).

Brem et al. teach the GM-CSF is a cytokine that systematically activate cytotoxic T lymphocytes which have shown to lead to the elimination of tumor cells in a potent and specific manner, by stimulating the growth and activity of several myeloid cells and playing a critical role in the migration and development of professional antigen presenting cells such as dendritic cells (see column 8, paragraph 2).

Given the teachings of combining FLT3-L and GM-CSF to treat cancer by Lyman et al. in combination with the teachings of Elliott et al. and Srivastava et al. that GM-CSF was potent in cancer vaccination, one of ordinary skill in the art would have combined FLT3-L, GM-CSF and tumor antigens to stimulate the hemopoietic and immune system of cancer patients, including the vaccination to tumor associated antigens. Given the teachings of stimulating the hemopoietic and immune systems with FLT3-L and GM-CSF with the teachings of administering tumor antigens to activate immune responses and antigen presentation, one of ordinary skill in the art would have had an expectation of success that the administration of FLT3-L and GM-CSF would increase the number of dendritic, as evidenced by the teachings of Brem et al. that GM-CSF activates immune responses via dendritic cells.

Given the teachings of the prior art to treat and augment immune responses in cancer patients and that the administration of cytokines and tumor antigens were based on variables and procedures known and practiced by the ordinary artisan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer tumor antigen at various times with respect to cytokine administration, including the administration of tumor antigen prior, concurrently and after cytokine administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to select a combination of cytokines, including FLT3-L and GM-CSF in combination with tumor antigens to treat human cancer; given the properties of said cytokines to augment immune responses including augmenting immune responses to cancer antigens and to stimulate hemopoietic cells to alleviate the effects of chemotherapy and radiation therapy in cancer patients.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.



Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
November 3, 2003